Review

Fermented Foods Strengthen Immunity against Viral Infections

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Abstract: Fermented foods have been shown to exert positive effects on gut health and immune function. However, the potential of fermented foods to enhance the bioavailability of bioactive compounds and support the growth of the beneficial microbial community's key factors in antiviral immunity remains less explored. In this review, we show that probiotic-fermented food improves the bioactive compound contents and is increasingly studied by basic and clinical researchers. Bioactive compounds, including phenolic, alkaloids, terpenoids, flavonoids, stilbenes, coumarins, tannins, anthocyanidins, flavones, isoflavonoids, and polyphenols, are increased in the probiotic fermentation conditions. Additionally, beneficial bacteria such as *Lactobacilli*, *Bifidobacteria*, *Pediococcus*, and *Weissella* are also restored in the fermented foods. These bioactive compounds, combined with a functional microbiota, play a role in preventing viral infections by targeting influenza, noroviruses (NoVs), Murine norovirus-1 (MNV-1), and COVID-19, while also stimulating the immune function of the host. It was suggested that clinical and pre-clinical investigations are required to explore the dose-response and duration efficacy of probiotic fermented foods against viral infections.

Keywords: fermented food; probiotics; bioactive compounds and antiviral potential

1. Introduction

Fermented foods have been produced and utilized as a diet since the development of human civilizations [1]. It is valuable for human health by relieving the blood cholesterol levels, and providing protection against pathogens, hazardous, and carcinogenic substances. Additionally, improving the digestibility for individuals with lactose intolerance (the fermentation process breaks down lactose into simpler sugars) [2,3]. The health-promoting effects of fermented foods are largely attributed to their rich content of bioactive compounds and beneficial native microbiota. These components act synergistically to enhance the nutritional profile and support overall human health and well-being [4]. For example, polyphenols, flavonoids, and antioxidants possess various health-promoting properties, including anti-inflammatory, anti-cancer, and immune-boosting effects [5–7]. Furthermore, angiotensin-1-converting enzymes [8], valyl-prolyl proline, and isoleucyl-prolyl-proline inhibitors have also been observed in fermented food [9]. These compounds can potentially treat hypertension and other associated health disorders. Similarly, the bioactive compounds and probiotic strains were found in the fermented food with antiviral potential and various mechanisms of action [3]. The application of these bioactive compounds and probiotics has shown promising efficacy against a wide range of viral infections, as demonstrated by both in vitro and in vivo studies [10,11]. These agents can enhance the host immune response through direct antiviral activity or by modulating immune function. Microbial fermentation provides a cost-effective and sustainable method for producing such beneficial metabolites, as it bypasses the need for complex pre-purification or hydrolysis steps required by other production techniques [12]. The fermentation can generate diverse amino acids; acidic, basic, or hydrophobic, that contribute not only to the nutritional profile but also to the aroma and functionality of the bioactive compounds in fermented foods [4,7,13]. Additionally, studies have shown that whey [14], and yogurt [15] fermented with *Lactobacillus* yield bioactive compounds that inhibit ACE (angiotensin-converting enzyme) activity, thereby modulating the function of toll-like receptor-4. Furthermore, research has identified a bioactive peptide (P18) produced by *Bacillus subtilis* within legume-based fermented foods [16]. This constitutes a significant component of the microbiota. Microflora of the *Bifidobacteria* and *Lactobacilli* might have the capability as anti-viral. For example, cell-free supernatants of *Lactobacillu*s spp., *Streptococcus thermophilus*, and *Bifidobacterium* bifidum cultures in yogurt produce metabolites that can prevent influenza virus infection [17,18]. Moreover, *Lactobacillus delbrueckii* subsp. bulgaricus releases the bacteriocin and was also found as an anti-influenza [18,19]. Clinical trials showed that the mucosal cells (IL-6 and IL-10) increase were observed in the clinical trials by using fermented food rich in bioactive and probiotics [20]. During the COVID-19 outbreak, several reports suggested that lower mortality rates observed in regions such as Asia, Africa, and parts of Europe may be partially linked to the widespread consumption of fermented foods in these populations [13,21–23]. In this review, we have thoroughly examined the bioavailability of bioactive compounds and the composition of probiotic bacterial communities in various fermented foods, highlighting their potential health-promoting benefits. Specifically, we analyzed how probiotic-fermented foods strengthen the body's defenses against viral infections, including respiratory ailments, gastrointestinal tract disorders, as well as infections caused by herpes simplex viruses. Notably, we have also examined emerging research regarding the potential role of fermented foods, including their probiotic components, in mitigating the impact of COVID-19. Moreover, this review provides a thorough analysis of the safety aspects surrounding fermented foods, addressing concerns related to contamination and spoilage, and outlining strategies for maintaining their integrity and nutritional value throughout the fermentation process and storage.

2. Microbiome and Functional Metabolites of Fermented Foods

Food fermentation and preservation methods significantly influence the flavor, texture, and shelf life of food products through various chemical transformations. Fermented foods derived from plant-based sources, dairy, alcoholic beverages, and marine products are widely consumed across the globe. Among these, fermented vegetables and fruits hold a prominent place in the history of human civilization, reflecting a long-standing tradition of dietary and cultural significance [1]. For example, sauerkraut (fermented cabbage), was commonly consumed in the Roman Empire [24], while *Jiangshui*, a traditional fermented vegetable in China, and Kimchi in Korea have been integral components of regional diets for centuries [25,26]. The fermented soybeans called "Miso and Natto" are used in Japan, while Indonesian Tempeh" [27] has different impacts on human health. Similarly, fermented alcoholic beverages from fruits, cereals, and milk were prepared under culture-dependent and independent techniques. For example, the fermentation of sake, flavored liquor, grape wine, and alcohol [28–30] under different cultures and parameters. Fermented food is a rich source for metagenomics, metaproteomics, metabolomics, and diverse meta-analyses studies, offering a plethora of opportunities for in-depth exploration. The various analyses employed to investigate fermented foods include:

2.1. Functional Microbiota

Dairy-fermented products have increased attention and are integral components of diets across the globe, as recognized by the International Dairy Federation (IDF) [31]. These products have been associated with potential health benefits, including enhanced insulin sensitivity, reduced cholesterol levels, and improved blood pressure regulation. *Airag*, a traditional fermented beverage from Mongolia made from unpasteurized mare's milk, has long been used for its purported therapeutic properties [32]. Probiotic strains such as *Streptococcus thermophilus* and *Lactobacillus delbrueckii*, commonly found in yogurt, contribute to improved digestion and the restoration of gut microbiota balance [29]. Overall, fermented foods are rich in probiotic bacterial strains and are utilized for various health-promoting functions, as outlined in Table 1. The microbial diversity in the fermented foods investigated, such as Firmicutes and Proteobacteria, were the pre-dominant phyla in the cheese, jueke, and koumiss. Similarly, *Lactobacillus*, *Leuconostoc*, *Weissella*, *Enterococcus*, and *Pediococcus* were observed in fermented vegetables and fruits [33,34]. In the cheese and Kefir samples, collectively *Lactococcus*, *Lactobacillus*, *Streptococcus*, *Acetobacter*, and *Leuconostoc* bacterial strains were found dominant [35]. Wu et al. demonstrated that *L. casei*, *L. helveticus*, and *Lactobacillus plantarum* were increased in koumiss [36]. Furthermore, *Enterococcus faecalis*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, *Lactobacillus plantarum*, *L. casei*, and *L. zeae* were reported in the Chinese sauerkraut [37]. It is suggested that the isolated probiotic strains from fermented food could be employed for basic and clinical research. Additionally, there is increasing focus on the demand for probiotics in the financial industry [1], owing to their physiological functions and potential to treat to different disorders. Yogurt, nutrition bars, snacks, infant foods, and numerous other products are now being fermented with probiotic bacterial strains to enhance their nutritional contents. For, example, gastroenterologists often prescribe commercial lyophilized pills for their patients. However, the scientific validation of probiotics in fermented foods for improving human health functions remains largely unexplored.

Table 1. Fermented foods and their impact on human health and host spots for various probiotic strains.

Fermented Food	Isolated Microorganisms	Functions	References
Koumiss	*Lactobacillus coryniformis*, *L. paracasei*, *L. kefiranofaciens L. curvatus L. fermentum*, *L. casei*, *L. helveticus*, *Lactobacillus plantarum*	i. Resistance to the low-acidic level ii. Antimicrobial activities	[36]
Kimchi	*L. casei* DK128, *Lactobacillus buchneri UA-1 and UA-2*	i. IgG antibodies rapid initiation. ii. Induce innate immune cells and cytokines iii. Metabolized uric acid	[38,39]
Jiangshui	*Lactobacillus*, *Limosilactobacillus fermentum*, *and L. bacilli*	i. Effective in hyperuricemia and gout ii. Provides coldness to the body	[25]
Yogurt	*Bifidobacterium animalis subsp. lactis*	i. Suppressing infection of *helicobacter pylori* ii. Lower the cholesterol levels in the serum iii. Stimulate the immune function iv. Improve lactose metabolism v. Antimicrobial, anticarcinogenic, antimutagenic, and antidiarrheal properties	[40,41]
Kefir	*L. acidophilus*, *Lactobacillus delbrueckii subsp. bulgaricus*, *Streptococcus thermophilus*, *L. crispatus*, *L. gasseri*, *L. jensenii*, *L. rhamnosus*	i. Act as lactose-tolerant and antibacterial ii. Antidiabetic iii. Suppressing tumors, and acting as an anti-hypertensive, anti-inflammatory, antioxidant, and carcinogenic	[40]
Mango pickle, Naan	Indigenous microflora, yeast	i. Appetizer and meal purposes ii. Increases elasticity in blood vessels and produce new blood cells	[42]
Sourdough (Khamir)	*Enterococcus mundtii*, and *Wickerhamomyces anomalus*, *Bacillus subtilis LZU-GM*	i. Contains gluten-degrading probiotics ii. Lowers the risk of cancer, aging, and arthritis iii. Relieves celiac disease	[43,44]
Fermented milk,	*Acinetobacter*, *Enterobacteriaceae*, *and Aeromonadaceae*	i. Immunomodulation and amelioration of colitis and diabetes ii. Used for gastrointestinal disorders, cancer, high cholesterol, and blood pressure	[45]
Shubat and Ayran	*Leuconostoc* and *Enterococcus*genera	Regulates bile salt tolerance and increases antibodies susceptibility	[46]
PaoCai	*Enterococcus faecalis*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, *L. plantarum*, *L. casei* and *L. zeae*	i. Appetizers and vitamin absorption ii. Anticancer effects	[37]
Fermented Portuguese olive	*L. plantarum and L. paraplantarum*	i. Affects acid and bile salt-tolerance ii. Simulated digestion iii. Exopolysaccharide producing abilities	[47,48]
Koumiss	*L. helveticus* and *L. delbrueckii*	i. Treat urogenital tract diseases and inflammatory disorders ii. Source of the biogenic amines	[49]
Raw camel milk	*L. fermentum*, *L. plantarum*, *L. casei*, *Lactococcus lactis*, *Enterococcus faecium*, and *S. thermophilus*	i. Monitoring diabetes including cholesterol levels, liver and kidney ailment ii. Oxidative stress decreases and heals the wound.	[50]
Pickle and cucumber		i. Prolongs shelf life ii. Reduces the toxic levels of protein and minerals	[42]
Tarhana	*Streptococcus thermophilus*, *L. fermentum*, *Enterococcus faecium*, *Pediococcus*	i. Rich source of minerals and nutrients ii. Affect pathogens and enhances shelf life	[51]

	pentosaceus, *Leuconostoc pseudomesenteroides*, *Weissella cibaria*, *L. plantarum*, *L.delbrueckii*, *Leuconostoc citreum*, *L. paraplantarum* and *L. casei.*		
Meju, *Doenjang*, *Jeotgal*, and *Mekgeolli*	*L.mesenteroides*, *L.plantarum*, *Aspergillus*, *Bacillus*, *Halomonas* sp., *Kocuria* sp., and *Saccharomyces cerevisiae*	i. Anticancer, anti-obesity, ii. Antioxidant, anti-inflammatory, and anti-diabetes	[52]
Dhokla	*L. plantarum* and *Weissella cibaria*	i. Antimicrobial activity ii. Infuence bile tolerance iii. Antibiotic susceptible	[53]
Cheese	*L. lactis L. delbrueckiiL. helveticus*, *L. casei*, *L. plantarum*, *L. salivarius*, *Leuconostoc* spp., *S. thermophilus*, *Ent. durans*, *Ent. faecium*, *Staphylococcus Brevibacterium linens*, *Propionibacterium freudenreichii*, *Penicillium camemberti*, *P. roqueforti*	i. Contains-aminobutyric acid (GABA). ii. Exopolysaccharides, peptides, vitamins, fatty acids, and organic acids iii. Anticancer effects	[54–56]
Pla-khao-sug	*Ped. cerevisiae*, *L. brevis*, *Staphylococcus* sp., *Bacillus* sp.	i. Boost the immune system ii. Suppression of pathogenic bacteria	[57]
Tapai Ubi	*Saccharomycopsis fibuligera*, *Amylomyces rouxii*, *Mu. circinelloides*, *Mu. javanicus*, *Hansenula* spp, *Rhi. arrhizus*, *Rhi. oryzae*, *Rhi. Chinensis*	i. Useful for nerve and muscle cells ii. Balancing microbial diversity and improving immunity	[58,59]
Tungrymbai	*B. subtilis*, *B. licheniformis*, *B. pumilus*	i. Isoflavone transformation and high antioxidants ii. Cheap source of proteins	[60,61]
Thua nao	*B. subtilis*, *B. pumilus*, *Lactobacillus* sp.	i. Contains pyrazine compounds and is rich in nutrients ii. Proteins supplement	[62,63]
Sufu	*Actinomucor elenans*, *Mucor. silvatixus*, *Mu. corticolus*, *Mu. hiemalis*, *Mu. praini*, *Mu. racemosus*, *Mu. subtilissimus*, *Rhiz. Chinensis*	i. Considered a healthy food because of its low cholesterol content ii. Act as sources of protein and calcium	[64,65]
Miso	*Ped. acidilactici*, *Leuc. paramesenteroides*, *Micrococcus halobius*, *Ped. halophilus*, *Streptococcus* sp., *Sacch. rouxii*, *Zygosaccharomyces rouxii*, *Asp. Oryzae*	i. Reduces cancer cell growth ii. Improves the digestive system iii. Lowers cholesterol levels.	[24,66]
Koozh and gherkin	*Lactobacillus and Weissella*	i. Achieves the maximum cholesterol reduction. ii. Exopolysaccharide source	[34]
Airag	*L. helveticus*, *L. kefiranofaciens*, *Bifidobacterium mongoliense*, and *Kluyveromyces marxianu*	i. Reduces thirst and hunger ii. Improves metabolism iii. Treats heart and lung diseases	[32]
Chhurpi	*L. farciminis*, *L. paracasei*, *L. biofermentans*, *L. plantarum*, *L. curvatus*, *L. fermentum*, *L. alimentarius*, *L. hilgardii*, *W. confusa*, *Ent. faecium*, *Leuc. Mesenteroides*	Constains high protein content and carbohydrates but low fat levels	[67,68]
Somar	*L. paracasei*, *L. Lactis*		[69]

Boza	*Lactobacillus* sp., *Lactococcus* sp., *Pediococcus* sp., and *Leuconostoc* sp.,	Contains biogenic amine content	[70,71]
Suan-tsai and fu-tsai	*Ent. faecalis*, *L. alimentarius*, *L. brevis*, *L. coryniformis*, *L. farciminis*, *L. plantarum*, *L. versmoldensis*, *Leuc. citreum*, *Leuc. mesenteroides*, *Leuc. pseudomesenteroides*, *P. pentosaceus*, *W. cibaria*, *W. paramesenteroides*	i. Remove cholesterol in vitro ii. Anti-oxidative and bile tolerance	[72]
Nem-chua	*L. pentosus*, *L. plantarum*, *L. brevis*, *L. paracasei*, *L. fermentum*, *L. acidipiscis*, *L. farciminis*, *L. rossiae*, *L. fuchuensis*, *L. namurensis*, *Lc. lactis*, *Leuc. citreum*, *Leuc. fallax*, *P. acidilactici*, *P. pentosaceus*, *P. stilesii*, *Weissella cibaria*, *W. paramesenteroides*	Inhibit the entrance of pathogenic microbes	[73]

2.2. Detection of Bioactive Compounds in Fermented Food

Analytical instruments, including gas chromatography with mass spectroscopy (GC-MS), High-performance liquid chromatography (HPLC), High-Resolution Nuclear Magnetic Resonance (H-NMR), and ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UHPLC-Q-TOF MS/MS, have been used mainly for the food metabolites analysis (Table 2). The bioactive compounds, including isothiocyanates and hexanoic acid, were found in the nozawana zuke in higher concentrations, while acetic acid, acetoin, and 2,3-butanedione were observed in low levels [74]. Barley fermented with *L. plantarum* dy-1 increased the indole-3-lactic acid, phenyl lactic acid, homovanillic acid, and cafestol, in contrast, amino acids, nucleotides, saccharides, and other organic acids declined [9]. 2,4-di-tert-butylphenol, fatty acid esters, and sugar derivatives were reported by using the GC-MS analysis in the fermented whole grain. Similarly, in potherb mustard pickle, volatile compounds such as allyl, butenyl, isobutanol, and phenyl ethyl groups were identified as substituents in the side chain (R-groups) [75]. Furthemore, γ-aminobutyric acid (GABA), acetoin, acetoacetate, cellobiose, and alanine were detected in the fermented cantaloupe using H-NMR [12]. The integrated lipomics and metabonomics methods were employed in the fermented milk. The results showed that 108 metabolites and 174 lipids were reported. A total of 35 bioactive compounds were observed in the *L. plantarum* P9 additive fermented milk, among which the high levels of detected compounds were fatty acids, peptides, and celluloses [76]. The efficient and sustainable fermented foods were identified through multiple meta-omics tools, as shown in Table 2.

Table 2. Bioactive compounds from fermented foods by using various techniques.

Fermented Foods	Metabolites	Techniques Use	References
Fermented cantaloupe juice	Isoleucine, valine, lactic acid, alanine, β-alanine, sucrose, erythritol, gluconic acid, GABA, alpha-aminobutyric acid, methionine, acetoin, acetoacetate, and phenylpropanoic acid	H-NMR	[77]
Fermented soybeans	Glucosyringic acid, engeletin, dihydroxy-4-phenyl coumarin, histidine, leucine, lysine, methionine, phenylalanine, and tryptophan	UPLC- QTOF MS/MS	[75]
Nozawana-zuke	Isothiocyanates, hexanoic acid, lactic acid, acetic acid, acetoin, 2,3-butanedione, glutamine, valine, leucine, isoleucine, choline, and methionine	NMR, SPME-GC/MS	[74]
Fermented milk	Fatty acids, peptides, amino acids, carbohydrates, vitamins, aldehydes, ketones	UPLC-QTOF-MS/MS	[76]
Fermented coffee brews	aromatic amino acid, catabolites, and hydroxy dodecanoic acid	LC-Q-TOF-MS/MS	[78]
Fermented camel and bovine milk	Fatty acyls, benzenoids, organ heterocyclic, organic acids and derivatives, phenylpropanoids, polyketides, glycerophospholipids, sterol lipids, polyketides, prenol	UPLC-QTOF	[79]

	lipids, organic oxygen, glycerolipids, organooxygen, alkaloids and derivatives, sphingolipids, hydrocarbons, nucleosides, nucleotides, and lignans, neolignans and related compounds, organosulfur compounds, hydrocarbon derivatives, organic nitrogen compounds		
Fermented goat milk	1-stearoyl-lysophosphatidylcholine, gaboxadol, guanine, cytosine, 4-acetamido benzoic acid, taurochenodeoxycholic acid, 2,6-dimorpholinopyrimidine-4-carboxylic acid, D-proline, DL-Glutamic acid, O-beta-D-glucosyl-*trans*-zeatin, N2-1-Carboxyethyl-N5 diamino methylene ornithine,	Q-HRMS-UPLC	[80]
Meju	Citric acid, pipecolic acid, glutamic acid, Isoleucine, Leucine, methionine, phenylalanine, tyrosine, proline, threonine, valine	UPLC-QTOF-MS	[81]
Cereal-based fermented foods	Volatiles (5 alcohols, dodecanoic acid, and 1,3-hexadiene) and the polyphenolic compounds gallic acid, epigallocatechin-gallate, epigallocatechin, flavonoids, protocatechuic acid, and total polyphenols	SPME-GC	[82]
Soymilk fermented	Amino acids, Organic acids, Sugars, Amines, Phenolic compounds, Lipids, Choline, and Trigonelline	H-NMR	[83]
Fermented Barley	Galactosamine, Maltose, Phenylacetic acid, Cuminaldehyde, Adenosine, Glucose 1-phosphate, Cafestol, Aspartic acid, Lysine, Tryptophan, Citric acid, Glucose Asparagine, Docosahexaenoic acid methyl ester, Histidine, Tyrosine, D-glucosamine-6-phosphate, Arginine, Fumaric acid, Benzaldehyde	UPLC-HRMS	[9]
Gochujangs	Amino acids, organic acids, sugar and sugar alcohol, flavonoids, lipids, and alkaloids	UPLC-QTOF-MS	[84]
Dry-fermented sausages	Amino acids, peptides, and analogs; carbohydrates; organic acids and derivatives; nucleosides, nucleotides, and analogues; fatty acids and miscellaneous	H-HR-MAS NMR	[85]
Sunki	Amino acids, organic acids, aldoses, alditol, and alcohol	NMR- and GC-MS	[86]
Koumiss	Glycerophospholipids, fatty acyls, sphingolipids, 1-glycerolipids, prenol lipids, organic acids, derivatives, organic oxygen, organoheterocyclic, benzenoids, organic nitrogen compounds, phenylpropanoids, polyketides, alkaloids, glycerophospholipids, fatty acyls, included amino acids, carboxylic acids and derivatives, benzenoids, glycosides, glycerolipids, alcohols, lactones, carbonyl compounds.	UPLC-QTOF-MS	[87]

3. Probiotic Fermentation of Food Increases Bioactive Compounds

The bioactive compounds rich in plants, dairy products, and microorganisms have a wide range of biological potential. For example, antidiabetic, immunity regulation, anticancer agents [2,88,89], and antiviral [3,13,23]. The functionality of the bioactive compounds is based on their structure. The triple helical *β*-glucans having a low molecular weight and higher m stiffness showed strong anti-tumor ability as compared to the lower and higher molecular weight and stiffness *β*-glucans [90]. Similarly, owing to the higher molecular weight (~10 MDa) of the *β*-(1-4)-D-mannans, they have stronger immune stimulation potential than lower molecular weight (~1.3 MDa) [91]. Fermentation of food with probiotic bacteria enhances its nutritional values, modifies chemical structure, and increases the availability of bioactive compounds compared to the unfermented and traditionally fermented products (Table 3). In plant cell walls, components such as cellulose, hemicellulose, and lignin form a compact structure that is difficult to hydrolyze. However, during fermentation, probiotic bacteria help break down these complex substances into simpler subunits, thereby increasing the levels of bioactive compounds [65]. The rhamnogalacturonan-I-type polysaccharides were degraded in the process of probiotic fermentation in the carrot pulp, which increased their biological function than unfermented carrot [92]. *L. casei*, *Enterococcus faecalis*, and *Candida utilis* were used in the fermentation of the *Semen vaccariae* and *Leonurus artemisia* Chinese herbal medicine, which increased 55.14%, 127.28%, 55.42%, and 49.21%, respectively, of the total flavonoids, alkaloids, polysaccharides, and saponins, compared with the natural herbs [93]. During the fermentation process of *Lespedeza cuneata* with *Lactobacillus pentosus*, the levels of quercetin and kaempferol were significantly increased by 242.9% and 266.7%, respectively. This enhancement augments the potential anti-aging properties of the fermented product [94].

The active regulation and metabolism of glucose and lipids in the probiotic-fermented carrot (*Daucus carota* L.) pulp enhance its functionality against diabetic effects compared to the unfermented pulp. It was also stated that polysaccharides of the probiotic-fermented pulp are more effective for type II diabetic rats than unfermented carrot pulp. This indicates that probiotic fermentation alters both the structure and concentration of bioactive compounds. When longan pulp is fermented by *L. fermentum*, the resulting polysaccharides exhibit characteristics such as lower molecular weight, viscosity, and particle size, yet higher solubility compared to those found in unfermented longan pulp. Therefore, *Leuconostoc mesenteroides* and *L. casei* were restored in the fermented longan pulp, which stimulates macrophage secretion of NO and IL-6 [95]. This indicates that the probiotic fermented food can lead to modification and enhancement in the physicochemical structure of the bioactivity of bioactive compounds. Additionally, probiotic fermentation extends the shelf life of foods and enhances their nutritional value. For example, *Bacteroides* spp could alter the structures of β-glucans, and glycans degraded into tri- and tetra-saccharides by *L. plantarum* [96]. The conversion of the baicalin to baicalein via its β-glucuronidase by *L. brevis*. *Saccharomyces boulardii* and *L. plantarum* bacteria tea fermentation were observed to improve the bioactive constituents, including methyl salicylate, geraniol, and 2-phenylethyl alcohol [97]. In the barley beverages, the contents of the total polyphenols and flavonoids were improved through fermention with strain *L. casei* and increased the antioxidant inhibitory function compared to the unfermented barley beverage [98]. Similarly, the lily bulb extract of *L. lancifolium* was cultivated with *S. cerevisae,* which increased polysaccharide production and the protein removal ratio compared to the unfermented. The carrot water-soluble and soybean-soluble polysaccharides, after the probiotic fermentation, enhanced immune regulation function [12]. Lily bulb fermented with *S. cerevisiae* showed a 91.46% protein removal ratio, while *L. plantarum* decreased the water-soluble polysaccharides by degrading them into monosaccharides. *Puerariae radix* was fermented with the *B. breve* increased 785% and 1010% of the daidzein and genistein contents which promoted the production of hyaluronic acid in the NHEK cells [99]. The incorporation of probiotic bacteria in food fermentation can reduce or change the toxic effects of the food.

Table 3. Probiotic fermentation of plant-based food increases bioactive compounds.

Fermented Agent	Probiotic Strains	Increase Compounds	References
Carrot pulp	*L. plantarum* NCU 116	Rhamnogalacturonan-I-type polysaccharides break down	[92]
Semen vaccariae and *Leonurus artemisia*	*L. casei*, *Enterococcus faecalis*, and *Candida utilis*	Total flavonoids, alkaloids, crude polysaccharides, and saponins contents	[100]
Lespedeza cuneata	*L. pentosus*	Quercetin and kaempferol	[101]
Daucus carota L.	*L. plantarum* NCU116	Effective regulation of glucose and lipid metabolism	[102]
Longan pulp	*L. fermentum*	Lower polysaccharide molecular weight, viscosity, and particle size, but higher solubility	[95]
Lily bulbs	*L. plantarum*	β-glucans and glycans degraded into tri- and tetra-saccharides	[103]
Lily bulbs	*Limosilactobacillus fermentum* GR-3	hexadecanoic acid methyl ester, 22-tetrahydroxy-5alpha-cholestan-6-one-3-O-beta-D-allopyranoside, 22-O-(6-deoxy-Alpha-L-mannopyranosyl)-3-O-beta-D-glucopyranosylpregn-5-en-20-one, 1-O-trans-feruloylglycerol, and 3,4 dihydroxybenzoic acid	[4]
Tea Plant	*Saccharomyces boulardii* and *L. plantarum*	methyl salicylate, geraniol, and 2-phenyl ethyl alcohol	[104]
Barley beverage	*L. casei*	total polyphenols and flavonoid contents	[98]
Lily bulbs	*L. lancifolium and S. cerevisae*	protein contents	[105]
Puerariae radix	*Bifidobactericum breve*	daidzein and genistein	[106]
Soybean	*Bacillus licheniformis*	Insulin-sensitizing action	[107]
Artemisia princeps	*L. plantarum* SN13T	catechol and seco-tanapartholide C	[108]

Panax notoginseng	*Streptococcus salivarius*, *L. helveticus*, *L.rhamnosus L.acidophilus*, *B. longum*, *B. catenulatum*, *B. breve* and *B. bifidum*	ginsenosides Rh (1) and Rg (3)	[109]
Polygonum cuspidatum	*Aspergillus niger* and Yeast	Production of resveratrol	[110]
Radix astragalus	*Aspergillus* spp.	3,4-di(4′-hydroxyphenyl) isobutyric acid	[111]
Cordyceps militaris	*Pediococcus pentosaceus*	β-glucan and cordycepin	[112]

4. Antiviral Properties of Fermented Food

Fermented foods and probiotic bacterial strains have received great attention for having the ability of high antiviral potential. The consumption of fermented food promotes the T-lymphocytes (CD^{3+}, CD^{16+}, and CD^{56+}) function and enhances pro-inflammatory cytokines to reduce the toxicity of the natural killer cells [113]. These functions of fermented food play a crucial role in controlling viral infections in both the alimentary and respiratory tracts. Furthermore, probiotic fermented foods support the digestive system and offer protection against influenza A viral infection [2]. Additionally, gastrointestinal viruses like rotaviruses, noroviruses, and enteroviruses can be controlled or minimized through the consumption of functional fermented foods [13]. Although the antiviral action of fermented products is not fully understood, studies have postulated that they may enhance the host's immunity through both direct and indirect viral contact (Figure 1). This mechanism showed that stimulation of the dendritic cells was increased because of the IgA secretion and IL-6 and IL-10 cells in the clinical trials by some probiotic strains from fermented food. IgA inhibition was caused to control the mucosal membrane attachment and attack of viruses [3]. Similarly, the lipopolysaccharides (LPS) prevent the viral ambition to the host cells. The detailed mechanism is presented in Table 4. It was found to inhibit influenza replication. The investigators stated that fermented foods comprising probiotics and bioactive compounds boost immune function and decrease casualty and viral infections.

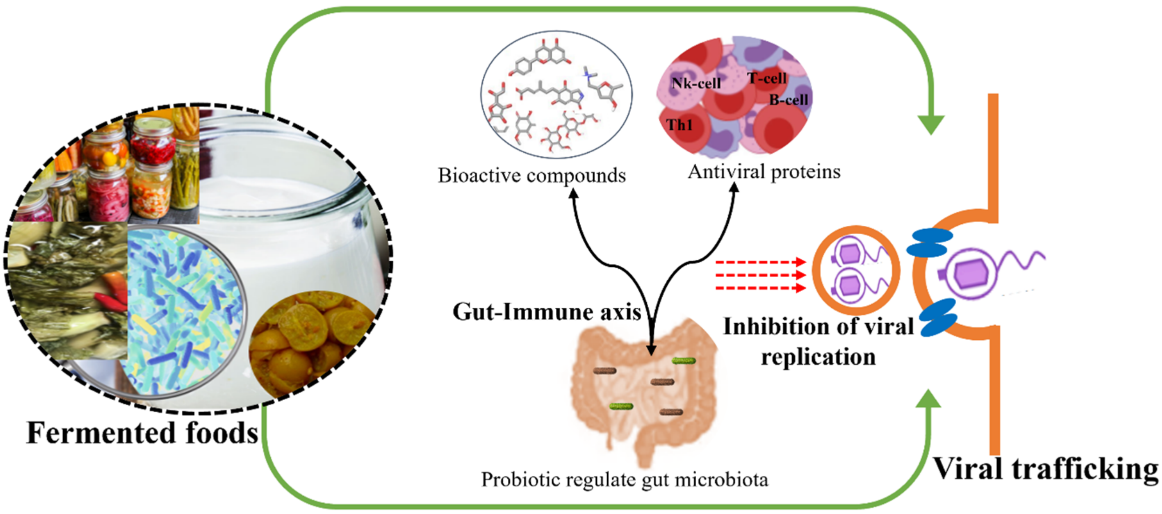

Figure 1. Fermented food promotes the immune system against viral infection via direct pathways (bioactive compounds such as organic acid, fatty acid, phenolic, and flavonoids) and indirectly by probiotics and gut microbiota.

4.1. Inhibition of Respiratory Virus

The influenza virus is a major cause of morbidity and mortality worldwide, primarily through respiratory tract infections. Emerging evidence suggests that the consumption of fermented vegetables, dairy products, and probiotic strains derived from fermented foods may help mitigate the effects of influenza. These dietary components have demonstrated the ability to enhance immune responses and may contribute to reducing the severity and duration of influenza infections. Therefore, incorporating fermented foods and probiotics into the diet represents a promising adjunct strategy for supporting immune defense against influenza. Thus, integrating fermented foods and probiotics into one's diet may offer a proactive approach to combating influenza-related health risks. In mice experiments, it was found that the influenza virus infections were controlled following administration of *Lactobacillus*, thereby increasing survival rates of the mice[22]. Similarly, Kimchi has a rich diversity of *L. caseai* Dk128 was employed in the mice experiment to control or protect against the influenza virus infection by quickly starting antibodies against IgG 1 and IgG2. As well as inducing the immune function of innate immune cells and cytokines [38]. This data indicates that the dose-dependent probiotic bacterial administration in fermented foods could also affect viral inhibition. Additionally, Korean fermented cabbage was screened with the *L. plantarum* DK119 to increase the cytokines IL-12 and IFN-c levels while decreasing the inflammation in the bronchoalveolar lavage fluids infected by the influenza virus [114]. *L. bulgaricus* OLL1073R-1 fermented yogurt was used by the elderly (67-74 years) of people, which can reduce the common cold by controlling the natural cell killers and protecting the immune system [115]. These findings indicate that incorporating probiotic-rich fermented foods into the diet could serve as a valuable complementary strategy to enhance antiviral defense, particularly against influenza. However, further clinical studies are warranted to confirm these effects in human populations and to determine optimal strains and dosages for therapeutic or preventive use.

4.2 Gastrointestinal Virus Suppression

Fermented foods have shown promising potential in suppressing gastrointestinal viral infections through multiple mechanisms. Probiotic strains commonly found in fermented products, such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* species, contribute to strengthening the intestinal barrier, modulating the gut microbiota, and enhancing mucosal immunity. These beneficial microbes can inhibit viral adhesion to intestinal epithelial cells, compete for nutrients and receptor sites, and produce antiviral metabolites such as lactic acid, short-chain fatty acids (SCFAs), and bacteriocins. Additionally, it was stated that the use of fermented food inhibited the rotaviruses, noroviruses, and enteroviruses [77]. However, before attachment and fusion with host cells, viruses can be affected by various physiological barriers, such as proteolytic enzymes, bile salts, and low pH conditions in the gastrointestinal tract [116]. Nonetheless, some enteric viruses exhibit resistance to these harsh conditions. Interestingly, in the early stages of infection, these viruses may be disrupted by fermented foods enriched with probiotic-derived bioactive compounds [113]. Strains *L. ruminis* and *B. longum* SPM1205, and SPM1206 were observed in the fermented food to control the rotavirus infection by inhibiting the Caco-2 cells. The replication of the murine norovirus-1 (MNV-1) was inhibited by the co-culture of *Bifidobacterium adolescentis* and the RAW 264.7 cells [117].

4.2. Herpes Simplex Virus

HSV-2 and HSV-1 were most frequently developed in the body, which causes herpes infection [118]. A group of probiotic strains, including *L. lactis* subspecies *lactis*, *L. rhamnosus*, *L. brevis*, and *L. crispatus,* respectively, can inhibit HSV-1 and HSV-2 replication. Similarly, bacteriocins purified from the *L. lactis* association with the cell-surface bacterial component and heat resistance repressed HSV-1 and HSV-2 activities [119]. In mammalian Vero and HeLa cell lines, the inhibitory activities of strain *L. crispatus* were investigated against HSV-2. The results showed that the viral entry was evaded due to the blockage of the HSv-2 in the cell surface during the colonization of *L. crispatus* [120] (Table 3)

4.3. COVID-19

The COVID-19 outbreak has gained serious critical significance, not only in the form of casualties but also caused financial crises worldwide back 2020–2021 and still [121]. It presents seasonal epidemics ranging from mild illness to fatal pulmonary diseases, which have historically been combated through vaccination to some extent and antiviral treatments. Nonetheless, these treatments commonly have limited effectiveness in persons with immunity suppression. Therefore, an appropriate strategy is needed to investigate the natural compounds or agents that suppress SARS-CoV-2 activity and promote the immune system because presently available antiviral agents are not efficacious and might have health side effects. Fermented food and food additives rich in natural compounds may boost the immune function and control the COVID-19 infection. In such cases, for example, it was reported that fermented milk product used on a daily basis is a capable choice to treat various viral infections [121]. The fermented foods are rich in the probiotic community-related Lactobacilli genus, which was found to be highly effective against viral infection (Table 3). The modification of the gut microbiota promotes the immune function in COVID-19-infected patients. The probiotics control the pathogenic communities over the friendly bacteria despite their age [21], because, in the COVID-19-infected individual, the pathogenic microbes stress the immune function. Therefore, the utilization of fermented foods and probiotics can help to minimize stress on the immune system, thereby enhancing its anti-viral capabilities. Kefir has gained considerable commercial interest due to its content of health-promoting probiotics and bioactive compounds that support gut microbiota balance and enhance immune function. For example, kefir consumption has been shown to stimulate the production of immune cells such as CD^{4+}, CD^{8+}, IgG^{+}, IgA^{+}, B, and T-cells, along with cytokines IL-2, IL-12, -γ. These immune components play critical roles in modulating immune responses and have been implicated in controlling cytokine storms during COVID-19 and other viral infections [22,52]. It has been proposed that incorporating probiotic bacterial strains into fermented foods to improve the bioavailability of beneficial compounds may offer a promising and supportive approach to the clinical management of COVID-19.

Table 4. Probiotic strains and bioactive compounds isolated from fermented food are effective against various kinds of viral infections.

Antiviral Agent	Target Viruses	References
P. pentosaceus, *W. cibaria*, *B. adolescentis*	Noroviruses and, murine-1virus	[18,122]
L. brevis and Secoiridoid glucosides	Herpes simplex virus type 2	[120]
L. acidophilus, *L. acidophilus*, *L. rhamnosus*, *L. plantarum*, *S. thermophilus*, and *B. bifidu*	Hepatitis C, Influenza virus,	[123,124]
L. acidophilus, *L. reuteri*, and *L. salivarius*	avian influenza virus	[125]
L. plantarum, *Enterococcus faecium L3*	Influenza virus, Coxsackie virus, Echovirus E7, and E19	[126]
Lactobacillus gasseri	Influenza A virus, Respiratory syncytial virus	[127]
L. reuteri ATCC 55730	Coxsackieviruses CA6 and Enterovirus 71	[128]
L. plantarum YU	Influenza A virus	[129]
L. plantarum DK119, *L. gasseri* SBT2055, *L. casei* DK128, Caffeic acid and glycyrrhizin	Influenza virus	[38,130,131]
Lactobacillus spp, *Bifidobacteria*	Vesicular stomatitis virus	[132,133]
Vitamin A, C, D, omega-3, fatty acids, and docosahexaenoic acid	Influenza and COVID-19	[134,135]
Taurine, creatine, carnosine, anserine, and 4-hydroxyproline	COVID-19	[136]
hexadecanoic acid methyl ester, 22-tetrahydroxy-5alpha-cholestan-6-one-3-O-beta-D-allopyranoside, 22-O-(6-deoxy-Alpha-L-mannopyranosyl)-3-O-beta-D-glucopyranosylpregn-5-en-20-one, 1-O-trans-feruloylglycerol, and 3,4 dihydroxybenzoic acid	Lung infection healing	[4]

5. Fermented Food Safety, Conclusion, and Future Prospects

The migration of people to urban areas has introduced several changes, including the need for food organization. Therefore, it is crucial to explore strategies for ensuring food security, in light of some outbreaks in recent years [31]. Several factors affect food security, including optimization parameters, economic pressure, and specific training for fermentation practices [137]. Among many food products, fermented food is highly produced at a small scale, and is considered tasty worldwide, although it may carry some risk. There are 3500 various types of fermented foods worldwide, accounting for up to 7.2% of the beverages in the period of 2018–2020 [1,138]. To boost consumer interest, attract entrepreneurs, and meet growing market demand, it's imperative to develop innovative approaches and product formulations in the realm of fermented foods. This might increase public demand and willingness to pay more attention to the use of fermented food and beverages such as grains, legumes, fruits, and vegetables. Fermented food product integration is important in national and global markets to sustain food care and production. Implementation of protective techniques can help reduce food-associated risks to public health, support free trade, improve food safety, and quality. Several probiotic strains can improve bioactive compounds and restore the abundance of beneficial microbiota in fermented food.

Furthermore, it is crucial to understand the dynamic interactions among metabolites and microbial diversity involved in the fermentation process to formulate microbiome models for assessing food quality and safety. Future research endeavors should explore and screen fermented products from diverse regions worldwide to identify probiotics and bioactive compounds that enhance immune system function. Additionally, fermented foods containing probiotics and bioactive compounds should be incorporated into clinical trials for viral infection management. Determining the optimal dose and duration of fermented food consumption is imperative. Nevertheless, the effects of bioactive compounds and probiotics present in fermented foods can enhance antiviral activities on host immune cells, both directly and indirectly. A significant challenge lies in the absence of an adequate database to profile microbiota and bioactive compounds in various fermented foods.

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